

Study Title
**COMBINED CHRONIC TOXICITY/ONCOGENICITY
STUDY 2-YEAR ORAL GAVAGE STUDY IN RATS**

Laboratory Project ID:

Volume 12 of 13

NUMBER OF PAGES IN VOLUME: 351

- TEST GUIDELINES:**
- U.S. EPA Health Effects Test Guidelines OPPTS 870.4300 Combined Chronic Toxicity/Carcinogenicity (1998)
 - OECD Guidelines for the Testing of Chemicals Section 4 (No. 453) Health Effects (2009)
 - JMAFF Japan Agricultural Chemicals Regulation Law 12 Nousan No. 8147 (2000)
 - EEC Methods for the Determination of Toxicity Method B.33 Combined Chronic/Carcinogenicity test, Directive 88/302/EC (1988)

AUTHOR:

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APPLICANT/SPONSOR:

PERFORMING LABORATORY:

WORK REQUEST NUMBER:

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Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1519	E	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1520	S	Macroscopic mammary gland	- swollen/thickened, tan, generalized, mild corresponds to antemortem observation (swelling)
1520	S	Microscopic adrenal glands kidneys	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, minimal
S - Scheduled necropsy E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1520	S	Microscopic liver	- focus of cellular alteration, basophilic, mild - focus of cellular alteration, eosinophilic, mild - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal
		lung	- histiocytosis, alveolar, minimal
		mammary gland	- hyperplasia, lobular, mild corresponds to macroscopic observation (mammary gland - swollen/thickened)
		pancreas	- adenoma, islet cell, benign, primary, incidental, not cause of death
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- within normal limits
1521	E	Macroscopic lymph node, axillary	- within normal limits draining node for mass a, right.

S - Scheduled necropsy
E - Euthanized *in extremis*

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Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1521	E	Macroscopic lymph node, inguinal skin, subcutis	- within normal limits draining node for mass b, right. - mass, tan, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 7.0 cm in diameter. - mass, tan, mass b, right inguinal area, present corresponds to antemortem observation (mass 2) approximately 11.0 x 6.0 x 4.0 cm.
1521	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - hematopoiesis, extramedullary, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1521	E	Microscopic eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, eosinophilic, mild - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - necrosis, focal, minimal - vacuolation, periportal, minimal - histiocytosis, alveolar, minimal
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1521	E	Microscopic lymph node, axillary lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - within normal limits - within normal limits - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b) - hyperplasia, lobular, minimal - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1521	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate
			- hyperplasia, epithelial cell, minimal
		thyroid gland	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1521	E	Microscopic tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - metaplasia, squamous, minimal - within normal limits - mammary tumor
1522	E	Macroscopic animal/whole body lymph node, inguinal pituitary gland skin, subcutis	- body fat depleted, moderate corresponds to antemortem observation (thin) - within normal limits draining node for mass a, left. - enlarged, red, severe - mass, tan, mass a, left anogenital region, present corresponds to antemortem observation (mass 1) approximately 3.0 cm in diameter.
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1522	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1522	E	Microscopic kidneys	- dilatation, tubular, bilateral, mild - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- within normal limits
		lung	- within normal limits
		lymph node, inguinal	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
		nerve, sciatic	- hyperplasia, lobular, mild
		nose, level a	- degeneration, axonal/myelin, minimal - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1522	E	Microscopic nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum	- within normal limits - within normal limits - within normal limits - cyst, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1522	E	Microscopic small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, c-cell, focal, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1523	E	Macroscopic lymph node, axillary lymph node, inguinal pituitary gland skin, subcutis	<ul style="list-style-type: none"> - within normal limits draining node for mass a, right, and mass c, right. - within normal limits draining node for mass b, right. - enlarged, red, mild - mass, black, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 4.5 x 4.0 x 2.0 cm. - mass, black, mass b, right anogenital region, present corresponds to antemortem observation (mass 2) approximately 4.5 x 4.5 x 3.0 cm. - mass, tan, mass c, right axillary area, present corresponds to antemortem observation (nodule) approximately 0.8 x 0.5 x 0.5 cm.
1523	E	Microscopic adrenal glands	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, moderate - hyperplasia, focal medullary, unilateral, moderate - hypertrophy, focal cortical, unilateral, minimal

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1523	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1523	E	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, inguinal lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - within normal limits - within normal limits - within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1523	E	Microscopic mammary gland	- adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b; skin, subcutis - mass c) - galactoceles, moderate corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal - degeneration, axonal/myelin, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1523	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1523	E	Microscopic thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, mild - adenoma, c-cell, benign, bilateral, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, minimal - within normal limits - mammary tumor
1524	E	Macroscopic lymph node, axillary lymph node, inguinal	- within normal limits draining node for mass a, left. - within normal limits draining node for mass b, right.
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1524	E	Macroscopic mammary gland pituitary gland skin, subcutis	- swollen/thickened, tan, generalized, moderate corresponds to antemortem observation (hair sparse swelling) - enlarged, moderate - mass, tan, mass b, right inguinal area, present approximately 1.0 cm in diameter. - mass, ulcerated, left axillary area, mass a, present corresponds to antemortem observation (mass 1) approximately 2.0 x 1.0 x 1.0, tan. - enlarged, horn, moderate
1524	E	uterus with cervix Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1524	E	Microscopic eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, inguinal	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, unilateral, minimal - pyelitis, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hyperplasia, bile duct, minimal - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1524	E	Microscopic lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	<ul style="list-style-type: none"> - within normal limits - within normal limits - adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b) - hyperplasia, lobular, mild corresponds to macroscopic observation (mammary gland - swollen/thickened) - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, minimal - within normal limits - atrophy, acinar, minimal - not examined - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1524	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1524	E	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, mild corresponds to macroscopic observation (uterus with cervix - enlarged)
1525	E	vagina Cause of Death Macroscopic lymph node, axillary pituitary gland skin, subcutis	- within normal limits - mammary tumor - within normal limits left, draining node for mass a. - enlarged, red, severe - mass, tan, mass a, left axillary area, present corresponds to antemortem observation (nodule swelling) approximately 1.0 x 1.0 x 0.5 cm.
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1525	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	 - angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - pyelitis, unilateral, minimal - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1525	E	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas	- within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - within normal limits - within normal limits - erythrocytosis/erythrophagocytosis, sinus, moderate - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1525	E	Microscopic parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1525	E	Microscopic stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - hyperplasia, c-cell, focal, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, mild - within normal limits - pituitary tumor
1526	E	Macroscopic lymph node, inguinal pituitary gland	- not identified, bilateral, no grade draining node for mass a, left and mass b, right. - enlarged, moderate

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1526	E	Macroscopic skin, subcutis	- mass, tan, mass a, left inguinal area, present corresponds to antemortem observation (mass 1) approximately 5.0 cm in diameter - mass, tan, mass b, right inguinal area, present approximately 2.0 cm in diameter.
1526	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - hyperplasia, focal cortical, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1526	E	Microscopic eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular	- within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, unilateral, minimal - mineralization, tubular, unilateral, minimal - pyelitis, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - vacuolation, periportal, minimal - histiocytosis, alveolar, minimal - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1526	E	Microscopic lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - exudate, nasal passage, moderate - inflammation, mild - exudate, nasal passage, moderate - inflammation, minimal - exudate, nasal passage, minimal - exudate, nasal passage, minimal - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1526	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1526	E	Microscopic thymus	- depletion, lymphoid, generalized, moderate
		thyroid gland	- hyperplasia, epithelial cell, minimal
		tongue	- adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		Cause of Death	- pituitary tumor
1527	E	Macroscopic ears	- nodule, tan, left, present corresponds to antemortem observation (nodule) approximately 0.4 cm in diameter.
		lymph node, axillary	- within normal limits draining node for mass b, right.

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1527	E	Macroscopic lymph node, inguinal pituitary gland skin, subcutis	- within normal limits draining node for mass a, right. - enlarged, red, moderate - mass, tan, mass a, right anogenital region, present corresponds to antemortem observation (mass 1) approximately 2.5 cm in diameter. - mass, tan, mass b, right axillary area, present corresponds to antemortem observation (mass 2) approximately 8.5 x 9.0 x 3.5 cm.
1527	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1527	E	Microscopic eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrima glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - degeneration/atrophy, retina, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1527	E	Microscopic liver	<ul style="list-style-type: none"> - focus of cellular alteration, basophilic, minimal - focus of cellular alteration, eosinophilic, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - vacuolation, periportal, minimal
		lung	<ul style="list-style-type: none"> - histiocytosis, alveolar, minimal
		lymph node, axillary	<ul style="list-style-type: none"> - within normal limits
		lymph node, inguinal	<ul style="list-style-type: none"> - within normal limits
		lymph node, mandibular	<ul style="list-style-type: none"> - erythrocytosis/erythrophagocytosis, sinus, minimal
		lymph node, mesenteric	<ul style="list-style-type: none"> - within normal limits
		mammary gland	<ul style="list-style-type: none"> - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b) - hyperplasia, lobular, mild
		nerve, sciatic	<ul style="list-style-type: none"> - within normal limits
		nose, level a	<ul style="list-style-type: none"> - within normal limits
		nose, level b	<ul style="list-style-type: none"> - within normal limits
		nose, level c	<ul style="list-style-type: none"> - within normal limits
		nose, level d	<ul style="list-style-type: none"> - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1527	E	Microscopic ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin skin, subcutis small intestine, duodenum small intestine, ileum small intestine, jejunum	- within normal limits - within normal limits - hyperplasia, acinar cell, focal, moderate - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - fibrosarcoma, malignant, primary, mortality-independent corresponds to macroscopic observation (ears - nodule) - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1527	E	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mammary tumor
1528	S	Macroscopic lymph node, inguinal	- not identified, right, no grade draining node for mass a.

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1528	S	Macroscopic skin, subcutis	- mass, tan, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 8.0 x 7.0 x 4.5 cm.
1528	S	spleen uterus with cervix Microscopic adrenal glands kidneys liver lung mammary gland pancreas	- enlarged, mild - enlarged, cervix, mild - hyperplasia, focal medullary, bilateral, mild - dilatation, tubular, bilateral, mild - edema, papilla, unilateral, minimal - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, acinar cell, focal, mild
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1528	S	Microscopic spleen stomach, nonglandular tongue uterus with cervix	- hematopoiesis, extramedullary, increased, mild corresponds to macroscopic observation (spleen - enlarged) - within normal limits - within normal limits - dilatation, gland/lumen, moderate corresponds to macroscopic observation (uterus with cervix - enlarged) - hyperplasia, cervical fibromuscular, mild corresponds to macroscopic observation (uterus with cervix - enlarged) - hyperplasia, squamous cell, minimal
1529	E	Macroscopic pituitary gland	- enlarged, moderate
1529	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1529	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1529	E	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - within normal limits - degeneration, cystic, focal, minimal - focus of cellular alteration, clear, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1529	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1529	E	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1530	E	Macroscopic pituitary gland	- enlarged, red, moderate
1530	E	Microscopic adrenal glands aorta bone marrow, femur	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - hyperplasia, focal cortical, unilateral, minimal - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1530	E	Microscopic bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon	- within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, focal, unilateral, minimal - within normal limits - within normal limits - hydronephrosis, unilateral, mild - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1530	E	Microscopic large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - vacuolation, periportal, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - atrophy, acinar, mild - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1530	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1530	E	Microscopic thymus	- depletion, lymphoid, generalized, moderate
			- hyperplasia, epithelial cell, minimal
		thyroid gland	- hyperplasia, c-cell, focal, unilateral, mild
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		Cause of Death	- pituitary tumor
1531	E	Macroscopic mammary gland	- swollen/thickened, tan, left axillary area, mild corresponds to antemortem observation (swelling)
		pituitary gland	- enlarged, red, severe
		stomach, nonglandular	- irregular surface, tan, mild

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1531	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - vacuolation, focal, unilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), moderate
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits
		kidneys	- mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1531	E	Microscopic lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - vacuolation, periportal, minimal - within normal limits - within normal limits - within normal limits - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (mammary gland - swollen/thickened) - hyperplasia, lobular, minimal - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1531	E	Microscopic oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic	- within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1531	E	Microscopic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - hyperplasia, epithelial, nonglandular, moderate corresponds to macroscopic observation (stomach, nonglandular - irregular surface) - inflammation, mild - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1532	S	Macroscopic lymph node, axillary	- within normal limits draining node for mass b, right.

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1532	S	Macroscopic lymph node, inguinal lymph node, mandibular pituitary gland skin, subcutis	<ul style="list-style-type: none"> - not identified, left, no grade draining node for mass c and mass d. - within normal limits draining node for mass a, right. - enlarged, red, mild - mass, tan, mass a, right lateral neck, present corresponds to antemortem observation (mass 1) approximately 6.0 x 5.0 x 2.5 cm. - mass, tan, mass b, right axillary area, present corresponds to antemortem observation (swelling) approximately 2.5 cm in diameter. - mass, tan, mass c, left inguinal area, present approximately 3.0 x 3.0 x 1.0 cm. - mass, tan, mass d, left anogenital region, present approximately 2.5 cm in diameter.
1532	S	Microscopic adrenal glands	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, mild
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1532	S	Microscopic kidneys	- mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal
		liver	- hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal
		lung	- within normal limits
		lymph node, axillary	- within normal limits
		lymph node, mandibular	- within normal limits
		mammary gland	- fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b; skin, subcutis - mass c; skin, subcutis - mass d)
		pancreas	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1532	S	Microscopic uterus with cervix	- within normal limits
1533	E	Macroscopic lymph node, axillary skin, subcutis	- within normal limits draining node for mass a, left. - mass, ulcerated, mass a, left axillary area, present corresponds to antemortem observation (mass 1) approximately 7.0 x 7.0 x 3.0 cm, tan.
1533	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1533	E	Microscopic eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, mandibular lymph node, mesenteric	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - within normal limits - within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1533	E	Microscopic mammary gland	- fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
		nerve, sciatic	- hyperplasia, lobular, minimal
		nose, level a	- degeneration, axonal/myelin, minimal
			- exudate, nasal passage, mild
			- foreign material, minimal plant.
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- atrophy, acinar, minimal
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
		pituitary gland	- within normal limits
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1533	E	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, c-cell, focal, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1533	E	Microscopic vagina Cause of Death	- within normal limits - mammary tumor
1534	D	Macroscopic pituitary gland	- enlarged, moderate
1534	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), severe - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i> D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1534	D	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic	- within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - exudate, luminal, minimal - inflammation, minimal - hyperplasia, bile duct, minimal - infiltration, mononuclear cell, minimal - vacuolation, periportal, mild - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1534	D	Microscopic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin	- within normal limits - within normal limits - mucus increased, mild - mucus increased, mild - cyst, unilateral, mild - hyperplasia, sex-cord/stromal, bilateral, mild - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1534	D	Microscopic small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - inflammation, acute, minimal - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1535	E	Macroscopic lymph node, axillary	- within normal limits draining node for mass a, left.
		skin, subcutis	- mass, ulcerated, mass a, left lateral neck, present corresponds to antemortem observation (mass 1) approximately 8.0 x 7.0 x 5.0 cm, tan.
1535	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate one medulla present
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1535	E	Microscopic eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, mandibular	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, tubular, bilateral, mild - edema, papilla, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - necrosis, hepatocytes, centrilobular, moderate - histiocytosis, alveolar, minimal - hyperplasia, lymphocyte/plasmacyte, medulla, mild - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1535	E	Microscopic lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual	- within normal limits - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, mild - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1535	E	Microscopic skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1535	E	Microscopic Cause of Death	- mammary tumor
1536	E	Macroscopic pituitary gland skin	- enlarged, moderate - hair sparse, generalized, mild corresponds to antemortem observation (hair sparse) most affected areas dorsal cervical, forelimbs bilateral and shoulders bilateral.
1536	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	- angiectasis/cystic degeneration, focal cortical, unilateral, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1536	E	Microscopic esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hydronephrosis, unilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - angiectasis, mild - hyperplasia, bile duct, minimal - histiocytosis, alveolar, minimal
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1536	E	Microscopic lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid	- within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1536	E	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1536	E	Microscopic uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - pituitary tumor
1537	E	Macroscopic pituitary gland	- enlarged, severe
1537	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1537	E	Microscopic eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimial glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - nephropathy, chronic progressive, bilateral, minimal - pyelitis, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - vacuolation, periportal, minimal - within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1537	E	Microscopic mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual	- hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, minimal - within normal limits one of pair present - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1537	E	Microscopic skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1537	E	Microscopic uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - pituitary tumor
1538	S	Macroscopic adrenal glands mammary gland ovaries pancreas spleen	- enlarged, left, moderate - swollen/thickened, mild right and left inguinal and axillary region mostly affected. - cyst, clear, left, mild - cyst, red, multiple, mild - focus/foci, white, mild
1538	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, severe corresponds to macroscopic observation (adrenal glands - enlarged) - atrophy, cortical, unilateral, moderate

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1538	S	Microscopic kidneys	<ul style="list-style-type: none"> - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - polyarteritis, bilateral, moderate renal artery.
		liver	<ul style="list-style-type: none"> - pyelitis, unilateral, minimal - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal
		lung	<ul style="list-style-type: none"> - hyperplasia, bile duct, minimal
		lymph node, mesenteric	<ul style="list-style-type: none"> - histiocytosis, alveolar, minimal
		mammary gland	<ul style="list-style-type: none"> - dilatation, sinus, mild - corresponds to macroscopic observation (pancreas - cyst) - fibroadenoma, benign, primary, incidental, not cause of death - corresponds to macroscopic observation (mammary gland - swollen/thickened)
		ovaries	<ul style="list-style-type: none"> - hyperplasia, lobular, moderate - corresponds to macroscopic observation (mammary gland - swollen/thickened) - cyst, unilateral, mild - corresponds to macroscopic observation (ovaries - cyst) - hyperplasia, sex-cord/stromal, unilateral, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1538	S	Microscopic pancreas	- atrophy, acinar, minimal - polyarteritis, moderate corresponds to macroscopic observation (pancreas - cyst)
		spleen	- fibrosis, capsular, mild corresponds to macroscopic observation (spleen - focus/foci, white)
		stomach, nonglandular tongue	- hematopoiesis, extramedullary, increased, minimal - within normal limits
		uterus with cervix	- within normal limits - dilatation, gland/lumen, minimal
1539	E	Macroscopic lung with bronchi	- discoloration, pink, azygous lobe, moderate
		lymph node, axillary	- within normal limits draining node for mass a, right and mass c, left.
		lymph node, mandibular	- within normal limits draining node for mass b, left.
		pituitary gland	- enlarged, mild

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1539	E	Macroscopic skin skin, subcutis	<ul style="list-style-type: none"> - abrasion/scab, right lateral head, moderate corresponds to antemortem observation (abrasion(s) swelling) - mass, tan, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 6.0 x 4.0 x 3.0 cm. - mass, tan, mass b, left lateral neck, present approximately 1.5 x 1.5 x 0.5 cm. - mass, tan, mass c, left axillary area, present corresponds to antemortem observation (swelling) approximately 1.0 cm in diameter.
1539	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - hyperplasia, granulocytic, mild - hyperplasia, granulocytic, minimal - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1539	E	Microscopic esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - pyelitis, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - vacuolation, periportal, mild - histiocytosis, alveolar, minimal
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1539	E	Microscopic lymph node, axillary lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands	- within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass b) - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass c) - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1539	E	Microscopic pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen	- within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - carcinoma, squamous cell, malignant, primary, mortality-independent corresponds to macroscopic observation (skin - abrasion/scab) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1539	E	Microscopic stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation Cause of Death	- within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - lung with bronchi - discoloration, pink - skin tumor
1540	E	Macroscopic lymph node, axillary	- within normal limits right is draining node for mass c.

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1540	E	Macroscopic lymph node, inguinal pituitary gland skin, subcutis	<ul style="list-style-type: none"> - within normal limits right is draining node for mass a, left is draining node for mass b. - enlarged, red, severe - mass, tan, mass b, left inguinal area, present corresponds to antemortem observation (mass 2) approximately 4.5 x 3.0 x 3.0 cm. - mass, tan, mass c, right axillary area, present corresponds to antemortem observation (mass 3) approximately 2.0 cm in diameter. - mass, ulcerated, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 2.5 x 2.0 x 1.5 cm and tan in color.
1540	E	Microscopic adrenal glands aorta bone marrow, femur	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, moderate - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1540	E	Microscopic bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	 - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1540	E	Microscopic liver	- focus of cellular alteration, basophilic, mild - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - vacuolation, periportal, minimal
		lung	- within normal limits
		lymph node, axillary	- not examined not found at the time of trimming
		lymph node, inguinal	- within normal limits
		lymph node, mandibular	- erythrocytosis/erythrophagocytosis, sinus, minimal
		lymph node, mesenteric	- within normal limits
		mammary gland	- adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b; skin, subcutis - mass c)
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1540	E	Microscopic nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1540	E	Microscopic spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, mild - within normal limits - mammary tumor
1541	S	Macroscopic adrenal glands	- enlarged, red, right, mild

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1541	S	Macroscopic lymph node, mandibular	- within normal limits draining node for mass a, right. draining node for mass b, left.
		mammary gland	- swollen/thickened, tan, generalized, moderate
		pituitary gland	- enlarged, red, mild
		skin, subcutis	- mass, tan, mass a, right lateral neck, present corresponds to antemortem observation (swelling) approximately 2.3 cm in diameter.
			- mass, tan, mass b, left lateral neck, present approximately 2.0 cm in diameter.
1541	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, severe corresponds to macroscopic observation (adrenal glands - enlarged)
		kidneys	- atrophy, cortical, unilateral, moderate - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1541	S	Microscopic liver	<ul style="list-style-type: none"> - focus of cellular alteration, basophilic, mild - focus of cellular alteration, clear, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - vacuolation, periportal, minimal
		lung	<ul style="list-style-type: none"> - within normal limits
		lymph node, mandibular	<ul style="list-style-type: none"> - within normal limits
		mammary gland	<ul style="list-style-type: none"> - adenocarcinoma, malignant, primary, incidental, not cause of death - corresponds to macroscopic observation (mammary gland - swollen/thickened) - fibroadenoma, benign, multiple, primary, mortality-independent - corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b) - hyperplasia, lobular, mild - corresponds to macroscopic observation (mammary gland - swollen/thickened)
		pancreas	<ul style="list-style-type: none"> - atrophy, acinar, minimal - hyperplasia, acinar cell, focal, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1541	S	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- within normal limits
1542	D	Macroscopic mammary gland pituitary gland skin	- swollen/thickened, generalized, mild - enlarged, red, severe - abrasion/scab, dorsal thoracic region, mild - hair sparse, neck, shoulder, right, mild corresponds to antemortem observation (hair sparse)
1542	D	Microscopic adrenal glands aorta	- within normal limits - within normal limits

S - Scheduled necropsy
D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1542	D	Microscopic bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon	- within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1542	D	Microscopic large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild corresponds to macroscopic observation (mammary gland - swollen/thickened) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1542	D	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse)
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1542	D	Microscopic thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation Cause of Death	- depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - skin - abrasion/scab - pituitary tumor
1543	S	Macroscopic adrenal glands pituitary gland	- enlarged, left, mild - cyst, clear, mild
1543	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - enlarged)
S - Scheduled necropsy D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1543	S	Microscopic kidneys liver lung pancreas pituitary gland stomach, nonglandular tongue uterus with cervix	- mineralization, pelvic, bilateral, minimal - hyperplasia, bile duct, minimal - within normal limits - atrophy, acinar, minimal - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - cyst) - within normal limits - within normal limits - within normal limits
1544	E	Macroscopic pituitary gland skin	- enlarged, severe - nodule, tan, nose/muzzle, present corresponds to antemortem observation (nodule) approximately 0.2 cm in diameter.
1544	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, moderate

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1544	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - degeneration/atrophy, retina, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, unilateral, minimal - pyelitis, unilateral, minimal - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1544	E	Microscopic large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hyperplasia, bile duct, minimal - histiocytosis, alveolar, minimal - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1544	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- hyperplasia, epidermal, moderate corresponds to macroscopic observation (skin - nodule)
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1544	E	Microscopic thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1545	D	Macroscopic eyes eyes, optic nerves eyes, retina	- absent/cannibalized, right, no grade corresponds to antemortem observation (cannibalized/partially cannibalized) - absent/cannibalized, right, no grade corresponds to antemortem observation (cannibalized/partially cannibalized) - absent/cannibalized, right, no grade corresponds to antemortem observation (cannibalized/partially cannibalized)
E - Euthanized <i>in extremis</i> D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1545	D	Macroscopic lacrimal glands, exorbital	- absent/cannibalized, right, no grade corresponds to antemortem observation (cannibalized/partially cannibalized)
		salivary gland, mandibular	- absent/cannibalized, bilateral, no grade
		salivary gland, parotid	- absent/cannibalized, bilateral, no grade corresponds to antemortem observation (cannibalized/partially cannibalized)
		salivary gland, sublingual	- absent/cannibalized, bilateral, no grade corresponds to antemortem observation (cannibalized/partially cannibalized)
1545	D	Microscopic adrenal glands	- within normal limits
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1545	D	Microscopic esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver	- within normal limits - within normal limits one of pair present - within normal limits one of pair present - not examined autolysis too severe for diagnosis - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1545	D	Microscopic lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular	- bacterial colonies, minimal areas with lysis of red blood cells indicative of dosing injury. - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined cannibalized
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1545	D	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea	- not examined cannibalized - not examined cannibalized - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1545	D	Microscopic ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - dosing injury
1546	S	Macroscopic pituitary gland uterus with cervix	- enlarged, red, mild - enlarged, horn, mild
1546	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate - hyperplasia, focal cortical, unilateral, minimal - pheochromocytoma, benign, unilateral, primary, incidental, not cause of death
S - Scheduled necropsy D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1546	S	Microscopic kidneys	- hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal
		liver	- fibrosis, minimal - focus of cellular alteration, eosinophilic, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - necrosis, focal, minimal
		lung	- within normal limits
		pancreas	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- dilatation, gland/lumen, mild corresponds to macroscopic observation (uterus with cervix - enlarged)
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1547	S	Macroscopic adrenal glands pituitary gland	- enlarged, left, mild - enlarged, severe
1547	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - enlarged)
		kidneys	- cyst, unilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal
		liver	- nephropathy, chronic progressive, unilateral, minimal - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal
		lung	- hyperplasia, bile duct, minimal - within normal limits
		pancreas	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1547	S	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- within normal limits
1548	E	Macroscopic lymph node, inguinal	- not identified, right, no grade draining node for mass a and mass c. draining node for mass b, left.

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1548	E	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - mass, tan, mass a, right anogenital region, present corresponds to antemortem observation (mass 1) approximately 9.0 x 5.0 x 3.0 cm. - mass, tan, mass b, left anogenital region, present approximately 3.0 cm in diameter. - mass, tan, mass c, right inguinal area, present approximately 2.0 x 1.5 x 1.0 cm.
1548	E	spleen uterus with cervix Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum	<ul style="list-style-type: none"> - enlarged, minimal - enlarged, horn, mild - angiectasis/cystic degeneration, focal cortical, bilateral, minimal - hyperplasia, focal cortical, bilateral, minimal - within normal limits - hyperplasia, granulocytic, mild - hyperplasia, granulocytic, minimal - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1548	E	Microscopic brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, minimal - vacuolation, periportal, minimal
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1548	E	Microscopic lung lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b; skin, subcutis - mass c) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1548	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild corresponds to macroscopic observation (spleen - enlarged)
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate hyperplasia, epithelial cell, minimal

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1548	E	Microscopic thyroid gland	- adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - hyperplasia, c-cell, focal, unilateral, mild
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- dilatation, gland/lumen, mild corresponds to macroscopic observation (uterus with cervix - enlarged)
		vagina	- granular cell tumor, benign, primary, incidental, not cause of death
		Cause of Death	- mammary tumor
1549	S	Macroscopic adrenal glands lymph node, inguinal	- focus/foci, red, left, mild - not identified, bilateral, no grade draining node for mass a, left and mass b, right.

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1549	S	Macroscopic pituitary gland skin, subcutis	<ul style="list-style-type: none"> - enlarged, mild - mass, tan, mass a, left anogenital region, present corresponds to antemortem observation (mass 1) approximately 5.0 x 4.0 x 3.0 cm. - mass, tan, mass b, right anogenital region, present approximately 1.5 cm in diameter.
1549	S	Microscopic adrenal glands kidneys liver lung	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - focus/foci, red) - hyperplasia, focal medullary, unilateral, minimal - mineralization, pelvic, unilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - focus of cellular alteration, basophilic, mild - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1549	S	Microscopic mammary gland	- fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b)
		pancreas	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- within normal limits
1550	D	Macroscopic lymph node, axillary	- within normal limits draining node for mass b, left.
		lymph node, inguinal	- not identified, left, no grade draining node for mass a.
		pituitary gland	- enlarged, red, severe
S - Scheduled necropsy D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1550	D	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - mass, tan, mass a, left inguinal area, present corresponds to antemortem observation (mass 1) approximately 4.0 x 3.0 x 2.0 cm. - mass, tan, mass b, left axillary area, present corresponds to antemortem observation (nodule) approximately 1.0 cm in diameter.
1550	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1550	D	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1550	D	Microscopic mammary gland	- adenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b) - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- cyst, unilateral, mild
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1550	D	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1550	D	Microscopic urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - metaplasia, squamous, minimal - within normal limits - pituitary tumor
1551	E	Macroscopic lung with bronchi lymph node, iliac ovaries	- focus/foci, red, multiple lobes, mild - within normal limits draining node for mass a, left. - mass, red, mass a, left, present approximately 2.0 cm in diameter.
1551	E	stomach, nonglandular Microscopic adrenal glands aorta bone marrow, femur	- focus/foci, tan, mild - angiectasis/cystic degeneration, focal cortical, unilateral, minimal - within normal limits - within normal limits
E - Euthanized <i>in extremis</i> D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1551	E	Microscopic bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - lymphoma, malignant, multicentric, fatal, positive cause of death - within normal limits - hyaline, droplets, increased, bilateral, mild - lymphoma, malignant, bilateral, multicentric, fatal, positive cause of death - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1551	E	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, iliac lymph node, mandibular lymph node, mediastinal lymph node, mesenteric mammary gland multicentric neoplasm nerve, sciatic nose, level a	- within normal limits - within normal limits - inflammation, minimal - focus of cellular alteration, basophilic, minimal - lymphoma, malignant, multicentric, fatal, positive cause of death - congestion, chronic passive, severe - lymphoma, malignant, multicentric, fatal, positive cause of death corresponds to macroscopic observation (lung with bronchi - focus/foci, red) - within normal limits - lymphoma, malignant, multicentric, fatal, positive cause of death - lymphoma, malignant, multicentric, fatal, positive cause of death slide 14. - erythrocytosis/erythrophagocytosis, sinus, mild - lymphoma, malignant, multicentric, fatal, positive cause of death - hyperplasia, lobular, mild - lymphoma, malignant, multicentric, fatal, positive cause of death - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1551	E	Microscopic nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin	- within normal limits - within normal limits - within normal limits - sex-cord/stromal tumor, malignant, unilateral, primary, incidental, not cause of death corresponds to macroscopic observation (ovaries - mass a) slide 15 and 26-1. - within normal limits - atrophy, acinar, minimal - fibrosis, minimal - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1551	E	Microscopic small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - erosion/ulcer, severe corresponds to macroscopic observation (stomach, nonglandular - focus/foci, tan) - erosion/ulcer, limiting ridge, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1551	E	Microscopic vagina Cause of Death	- within normal limits - lymphoid tumor
1552	E	Macroscopic pituitary gland	- enlarged, severe
1552	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1552	E	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b	- within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, mild - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1552	E	Microscopic nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1552	E	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - within normal limits - within normal limits - pituitary tumor
1553	S	Macroscopic adrenal glands	- enlarged, left, mild

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1553	S	Macroscopic lymph node, axillary lymph node, inguinal pituitary gland skin, subcutis	- within normal limits draining node for mass b, right. draining node for mass c, left. - within normal limits draining node for mass a, right. - enlarged, red, moderate - mass, tan, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 2.0 cm in diameter. - mass, tan, mass b, right axillary area, present approximately 1.2 cm in diameter. - mass, tan, mass c, left axillary area, present approximately 1.8 cm in diameter.
1553	S	Microscopic adrenal glands kidneys	- angiectasis/cystic degeneration, focal cortical, bilateral, severe corresponds to macroscopic observation (adrenal glands - enlarged) - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1553	S	Microscopic liver lung lymph node, axillary lymph node, inguinal mammary gland pancreas pituitary gland stomach, nonglandular tongue uterus with cervix	<ul style="list-style-type: none"> - infiltration, mononuclear cell, minimal - vacuolation, periportal, minimal - within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass c) - fibroadenoma, benign, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass b) - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - dilatation, gland/lumen, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1554	E	Macroscopic lymph node, inguinal	- within normal limits draining node for mass a, right.
		pituitary gland	- enlarged, red, severe
		skin, subcutis	- mass, tan, mass a, right anogenital region, present approximately 3.5 cm in diameter.
1554	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), moderate
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1554	E	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, inguinal lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, unilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, eosinophilic, mild - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1554	E	Microscopic mammary gland	- fibroadenoma, benign, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1554	E	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1554	E	Microscopic vagina Cause of Death	- within normal limits - pituitary tumor
1555	D	Macroscopic pituitary gland skin thymus	- enlarged, red, moderate - hair sparse, dorsal cervical region, dorsal head, mild corresponds to antemortem observation (hair sparse) - small, moderate
1555	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits
E - Euthanized <i>in extremis</i> D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1555	D	Microscopic eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, eosinophilic, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1555	D	Microscopic nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1555	D	Microscopic skin	- alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse)
			- cyst, keratin, minimal
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe corresponds to macroscopic observation (thymus - small)
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1555	D	Microscopic uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - pituitary tumor
1556	E	Macroscopic lymph node, inguinal lymph node, mandibular pituitary gland	- not identified, right, no grade draining node for mass c and mass d. draining node for mass a, left. - within normal limits draining node for mass b, right. - enlarged, mild
E - Euthanized <i>in extremis</i> D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1556	E	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - mass, tan, right anogenital region, mass c, present approximately 1.2 cm in diameter. - mass, tan, right inguinal area, mass d, present approximately 1.4 cm in diameter. - mass, tan, right lateral neck, mass b, present corresponds to antemortem observation (nodule) approximately 1.2 cm in diameter. - mass, ulcerated, left anogenital region, mass a, present corresponds to antemortem observation (mass 1 skin discolored) approximately 3.0 cm in diameter, tan.
1556	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1556	E	Microscopic esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, inguinal lymph node, mandibular	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1556	E	Microscopic lymph node, mesenteric mammary gland	- within normal limits - adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b; skin, subcutis - mass c; skin, subcutis - mass d) - hyperplasia, lobular, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- atrophy, acinar, mild
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1556	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1556	E	Microscopic thymus	- depletion, lymphoid, generalized, severe - hyperplasia, epithelial cell, minimal
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- metaplasia, squamous, minimal
		vagina	- within normal limits
		Cause of Death	- mammary tumor
1557	E	Macroscopic pituitary gland	- enlarged, red, severe
		stomach, nonglandular	- irregular surface, mild
1557	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1557	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, transitional cell, unilateral, mild - mineralization, pelvic, bilateral, minimal - pyelitis, bilateral, mild - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1557	E	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas	- within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - infiltration, mononuclear cell, minimal - necrosis, focal, minimal - vacuolation, periportal, mild - within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1557	E	Microscopic parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular	- not examined - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1557	E	Microscopic stomach, nonglandular	- hyperplasia, epithelial, nonglandular, moderate corresponds to macroscopic observation (stomach, nonglandular - irregular surface) - inflammation, mild corresponds to macroscopic observation (stomach, nonglandular - irregular surface)
		thymus	- depletion, lymphoid, generalized, moderate
		thyroid gland	- carcinoma, c-cell, malignant, unilateral, primary, incidental, not cause of death
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- dilatation, gland/lumen, mild
		vagina	- within normal limits
		Cause of Death	- pituitary tumor
1558	E	Macroscopic adrenal glands	- enlarged, left, minimal

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1558	E	Macroscopic cavity, thoracic kidneys liver lymph node, axillary lymph node, inguinal pituitary gland skin, subcutis spleen	- fluid, clear, minimal approximately 1.0 ml. - discoloration, tan, bilateral, minimal - discoloration, tan, multiple lobes, minimal - within normal limits draining node for mass a, left. - within normal limits draining node for mass b, left. - enlarged, red, moderate - mass, scabbed, mass a, left axillary area, present corresponds to antemortem observation (mass 1) approximately 20.0 cm in diameter, tan. - mass, tan, mass b, left anogenital region, present approximately 2.0 x 1.0 x 1.0 cm. - enlarged, mild
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1558	E	Microscopic adrenal glands	- adenoma, cortical, benign, unilateral, primary, incidental, not cause of death corresponds to macroscopic observation (adrenal glands - enlarged) - angiectasis/cystic degeneration, focal cortical, unilateral, minimal - hematopoiesis, extramedullary, bilateral, minimal - hyperplasia, focal cortical, bilateral, mild
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1558	E	Microscopic harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung	<ul style="list-style-type: none"> - within normal limits - within normal limits - within normal limits - dilatation, tubular, bilateral, mild - hyaline, droplets, increased, bilateral, mild - corresponds to macroscopic observation (kidneys - discoloration, tan) - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - degeneration, cystic, focal, minimal - infiltration, mononuclear cell, minimal - necrosis, hepatocytes, centrilobular, mild - corresponds to macroscopic observation (liver - discoloration, tan) - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1558	E	Microscopic lymph node, axillary lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - adenocarcinoma, malignant, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass b) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1558	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		skin, subcutis	- fibrosarcoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild corresponds to macroscopic observation (spleen - enlarged)
		stomach, glandular	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1558	E	Microscopic stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, minimal - within normal limits - fibrosarcoma/fibroma
1559	S	Macroscopic lymph node, inguinal	- not identified, bilateral, no grade draining node for mass a, right. draining node for mass b, left.
S - Scheduled necropsy E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1559	S	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - mass, tan, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 5.5 x 5.5 x 3.0 cm. - mass, tan, mass b, left inguinal area, present approximately 1.0 cm in diameter.
1559	S	Microscopic adrenal glands kidneys liver lung	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, unilateral, moderate - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - focus of cellular alteration, basophilic, mild - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - vacuolation, periportal, minimal - histiocytosis, alveolar, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1559	S	Microscopic mammary gland	- adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b)
		pancreas	- within normal limits
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- within normal limits
1560	E	Macroscopic adrenal glands	- enlarged, tan, right, mild
		lymph node, mandibular	- not identified, bilateral, no grade draining node for mass a.
		pituitary gland	- enlarged, tan, mild
		skin, subcutis	- mass, ulcerated, mass a, ventral neck, present corresponds to antemortem observation (mass 1) approximately 5.0 x 4.5 x 3.0 cm, tan.

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1560	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, moderate corresponds to macroscopic observation (adrenal glands - enlarged)
		aorta	- hyperplasia, focal cortical, unilateral, minimal
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- hyperplasia, granulocytic, mild
		bone, femur	- hyperplasia, granulocytic, mild
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1560	E	Microscopic kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c	- mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - within normal limits - not examined - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1560	E	Microscopic nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1560	E	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, epithelial cell, minimal - adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mammary tumor
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1566	D	Macroscopic skin	- hair sparse, dorsal cervical region, dorsal head, moderate corresponds to antemortem observation (hair sparse)
1566	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1566	D	Microscopic joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c	- within normal limits - mineralization, pelvic, bilateral, mild - mineralization, tubular, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - infiltration, mononuclear cell, minimal - within normal limits lysis of red blood cells within capillaries. - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1566	D	Microscopic nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical	- within normal limits - within normal limits - within normal limits - polyarteritis, mild - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1566	D	Microscopic spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dosing injury
1567	D	Macroscopic kidneys	- irregular surface, bilateral, mild
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1567	D	Macroscopic lung with bronchi pituitary gland skin	- discoloration, red, multiple lobes, moderate - enlarged, minimal - hair sparse, head, right lateral thorax, moderate corresponds to antemortem observation (hair sparse)
1567	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1567	D	Microscopic heart joint, tibiofemoral kidneys lacrima glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic	- cardiomyopathy, minimal - within normal limits - mineralization, pelvic, unilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - infiltration, mononuclear cell, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1567	D	Microscopic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1567	D	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - polyp, stromal, benign, primary, incidental, not cause of death - within normal limits - lung with bronchi - discoloration, red - pituitary gland - enlarged - dosing injury
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1573	E	Macroscopic adrenal glands brain kidneys liver lung with bronchi lymph node, axillary lymph node, iliac lymph node, inguinal lymph node, mesenteric pancreas pituitary gland	- enlarged, left, mild - discoloration, tan, moderate - discoloration, tan, pelvis, bilateral, mild - focus/foci, tan, median lobe, right lateral lobe, mild - nodule, tan, left lateral lobe, present approximately 0.4 cm in diameter. - discoloration, pink, multiple lobes, mild - within normal limits draining node for mass b, right. - within normal limits draining node for mass d. - not identified, left, no grade draining node for mass a. - within normal limits draining node for mass c. - mass, tan, mass c, present approximately 0.6 cm in diameter. - enlarged, red, severe

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1573	E	Macroscopic skin, subcutis	- mass, tan, mass b, right axillary area, present corresponds to antemortem observation (nodule) approximately 2.0 cm in diameter. - mass, ulcerated, mass a, left inguinal area, present corresponds to antemortem observation (mass 1) approximately 7.5 x 6.0 x 3.0 cm, tan.
1573	E	uterus with cervix	- mass, tan, mass d, present approximately 4.0 cm in diameter.
		Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, severe corresponds to macroscopic observation (adrenal glands - enlarged)
		aorta	- within normal limits
		bone marrow, femur	- hyperplasia, granulocytic, mild
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1573	E	Microscopic brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital	- compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - degeneration/atrophy, retina, unilateral, mild - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - dilatation, tubular, bilateral, mild corresponds to macroscopic observation (kidneys - discoloration, tan) - edema, papilla, bilateral, mild corresponds to macroscopic observation (kidneys - discoloration, tan) - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1573	E	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, iliac lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - within normal limits - within normal limits - adenoma, hepatocellular, benign, primary, incidental, not cause of death corresponds to macroscopic observation (liver - nodule) - focus of cellular alteration, basophilic, minimal - hypertrophy, hepatocyte, centrilobular, mild - necrosis, hepatocytes, centrilobular, mild corresponds to macroscopic observation (liver - focus/foci, tan) - histiocytosis, alveolar, minimal - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1573	E	Microscopic mammary gland	<ul style="list-style-type: none"> - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b) - hyperplasia, lobular, mild
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	- within normal limits
		pituitary gland	<ul style="list-style-type: none"> - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1573	E	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1573	E	Microscopic uterus with cervix	- carcinoma, squamous cell, malignant, primary, incidental, not cause of death corresponds to macroscopic observation (uterus with cervix - mass d)
		vagina	- within normal limits
		non-correlated macro observation	- brain - discoloration, tan - lung with bronchi - discoloration, pink - pancreas - mass c - mammary tumor
		Cause of Death	
1574	E	Macroscopic pituitary gland	- enlarged, red, severe
1574	E	Microscopic adrenal glands	- adenoma, cortical, benign, unilateral, primary, incidental, not cause of death - angiectasis/cystic degeneration, focal cortical, unilateral, moderate

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1574	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1574	E	Microscopic large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1574	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- hyperplasia, epithelial, limiting ridge, minimal
		thymus	- depletion, lymphoid, generalized, moderate

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1574	E	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- hyperplasia, c-cell, focal, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1575	D	Macroscopic all tissues	- within normal limits
1575	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i> D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1575	D	Microscopic bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - dilatation, tubular, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - necrosis, papillary, bilateral, severe - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1575	D	Microscopic pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, lymphoid, medulla, mild
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1575	D	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - hyperplasia, simple transitional cell, mild - within normal limits - within normal limits - kidney inflammation/necrosis
1576	S	Macroscopic kidneys liver lymph node, inguinal skin, subcutis	- irregular surface, bilateral, mild - focus/foci, tan, multiple lobes, mild - not identified, left, no grade draining node for mass a. - mass, tan, mass a, left inguinal area, present corresponds to antemortem observation (mass 1) approximately 5.0 x 9.0 x 8.0 cm.
S - Scheduled necropsy D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1576	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1576	S	Microscopic kidneys	<ul style="list-style-type: none"> - dilatation, tubular, bilateral, mild - edema, papilla, bilateral, minimal - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - corresponds to macroscopic observation (kidneys - irregular surface)
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1576	S	Microscopic liver	<ul style="list-style-type: none"> - adenoma, hepatocellular, benign, primary, incidental, not cause of death - corresponds to macroscopic observation (liver - focus/foci, tan) - degeneration, cystic, focal, minimal - focus of cellular alteration, basophilic, minimal - focus of cellular alteration, eosinophilic, moderate - corresponds to macroscopic observation (liver - focus/foci, tan) - hypertrophy, hepatocyte, panlobular, mild - infiltration, mononuclear cell, minimal - necrosis, individual hepatocyte, mild - histiocytosis, alveolar, minimal
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- fibroadenoma, benign, primary, mortality-independent
		mammary gland	- corresponds to macroscopic observation (skin, subcutis - mass a)
		nerve, sciatic	- hyperplasia, lobular, mild
		nose, level a	- degeneration, axonal/myelin, minimal
		nose, level b	- within normal limits
			- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1576	S	Microscopic nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1576	S	Microscopic spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - hyperplasia, squamous cell, mild - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - polyp, stromal, benign, primary, incidental, not cause of death - within normal limits
1577	E	Macroscopic lung with bronchi	- discoloration, tan, multiple lobes, moderate

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1577	E	Macroscopic lymph node, iliac lymph node, inguinal skin, subcutis	- within normal limits draining node for mass a, left. - not identified, right, no grade draining node for mass b. - abscess, left inguinal area, moderate corresponds to antemortem observation (nodule) - mass, tan, mass a, left anogenital region, present corresponds to antemortem observation (mass 1 swelling) approximately 5.0 cm in diameter. - mass, tan, mass b, right inguinal area, present corresponds to antemortem observation (mass 2) approximately 4.5 cm in diameter.
1577	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate - hyperplasia, focal medullary, unilateral, minimal - pheochromocytoma, benign, unilateral, primary, incidental, not cause of death

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1577	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- within normal limits - hyperplasia, granulocytic, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1577	E	Microscopic kidneys	<ul style="list-style-type: none"> - cyst, unilateral, mild - dilatation, tubular, bilateral, mild - edema, papilla, bilateral, minimal - mineralization, pelvic, unilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	<ul style="list-style-type: none"> - degeneration, cystic, focal, mild - hyperplasia, bile duct, mild - hypertrophy, hepatocyte, panlobular, mild - necrosis, hepatocytes, centrilobular, mild
		lung	- histiocytosis, alveolar, minimal
		lymph node, iliac	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1577	E	Microscopic mammary gland	- adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - abscess; skin, subcutis - mass a; skin, subcutis - mass b)
		nerve, sciatic	- hyperplasia, lobular, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1577	E	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - hyperplasia, epithelial, limiting ridge, minimal - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1577	E	Microscopic uterus with cervix vagina non-correlated macro observation Cause of Death	- metaplasia, squamous, minimal - within normal limits - lung with bronchi - discoloration, tan - mammary tumor
1578	S	Macroscopic kidneys	- irregular surface, bilateral, mild
1578	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1578	S	Microscopic eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrima glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - edema, papilla, bilateral, mild - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, mild - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1578	S	Microscopic liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid	- hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, mild - within normal limits - within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - cyst, minimal - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1578	S	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1578	S	Microscopic uterus with cervix	- hyperkeratosis, minimal - hyperplasia, squamous cell, mild
		vagina	- within normal limits
1579	E	Macroscopic kidneys	- irregular surface, bilateral, mild
		lymph node, axillary	- not identified, right, no grade draining node for mass a
		pituitary gland	- enlarged, red, moderate
		skin	- hair sparse, ventral abdomen, mild corresponds to antemortem observation (hair sparse)
		skin, subcutis	- mass, ulcerated, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 6.0 x 5.0 x 4.0 cm, tan
1579	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - hyperplasia, focal medullary, unilateral, moderate

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1579	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1579	E	Microscopic kidneys	<ul style="list-style-type: none"> - dilatation, tubular, bilateral, minimal - edema, papilla, bilateral, mild - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - corresponds to macroscopic observation (kidneys - irregular surface)
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- hypertrophy, hepatocyte, centrilobular, minimal
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1579	E	Microscopic mammary gland	- fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- not examined
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1579	E	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea	- within normal limits - within normal limits - alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - hyperplasia, epithelial, limiting ridge, minimal - depletion, lymphoid, generalized, moderate - hyperplasia, lymphoid, medulla, mild - within normal limits - hyperplasia, squamous cell, mild - inflammation, subacute/chronic, mild - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1579	E	Microscopic ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - hyperplasia, endometrial, mild - hyperplasia, squamous cell, mild - within normal limits - mammary tumor
1580	E	Macroscopic pituitary gland	- enlarged, moderate
1580	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1580	E	Microscopic esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, mild - nephropathy, chronic progressive, bilateral, mild - pyelitis, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1580	E	Microscopic lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid	- within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - atrophy, acinar, minimal - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1580	E	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, c-cell, focal, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1580	E	Microscopic vagina Cause of Death	- within normal limits - pituitary tumor
1581	S	Macroscopic all tissues	- within normal limits
1581	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	- hyperplasia, focal medullary, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1581	S	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland	- within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - edema, papilla, bilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1581	S	Microscopic nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum	- degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1581	S	Microscopic small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1582	E	Macroscopic kidneys	- irregular surface, bilateral, mild

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1582	E	Macroscopic pituitary gland	- enlarged, severe
1582	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1582	E	Microscopic kidneys	<ul style="list-style-type: none"> - dilatation, tubular, bilateral, minimal - edema, papilla, bilateral, mild - hyperplasia, transitional cell, bilateral, mild - mineralization, pelvic, bilateral, mild - nephropathy, chronic progressive, bilateral, mild - corresponds to macroscopic observation (kidneys - irregular surface)
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	<ul style="list-style-type: none"> - adenoma, hepatocellular, benign, primary, incidental, not cause of death - degeneration, cystic, focal, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal
		lung	<ul style="list-style-type: none"> - infiltration, mononuclear cell, minimal - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1582	E	Microscopic lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular	- within normal limits - within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - atrophy, acinar, minimal - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1582	E	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, epithelial cell, minimal - hyperplasia, c-cell, focal, unilateral, minimal - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1582	E	Microscopic urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - pituitary tumor
1583 ^r	E	Macroscopic kidneys lymph node, axillary lymph node, inguinal pituitary gland	- irregular surface, bilateral, mild - enlarged, right, mild draining node for mass a. - not identified, right, no grade draining node for mass b. - enlarged, mild

E - Euthanized *in extremis*
^r Replacement animal

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1583 ^r	E	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - abscess, left axillary area, mild - mass, red, mass b, right anogenital region, present corresponds to antemortem observation (mass 2) approximately 2.0 cm in diameter. - mass, ulcerated, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 2.5 x 4.0 x 1.0 cm, tan.
1583 ^r	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves	<ul style="list-style-type: none"> - hematopoiesis, extramedullary, bilateral, minimal - within normal limits - hyperplasia, granulocytic, mild - hyperplasia, granulocytic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

^r Replacement animal

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1583 ^r	E	Microscopic eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrima glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, tubular, bilateral, mild - edema, papilla, bilateral, mild - hydronephrosis, unilateral, mild - hyperplasia, transitional cell, bilateral, minimal - mineralization, tubular, bilateral, mild - nephropathy, chronic progressive, bilateral, moderate corresponds to macroscopic observation (kidneys - irregular surface) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*
^r Replacement animal

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1583 ^r	E	Microscopic liver	- hematopoiesis, extramedullary, minimal - hypertrophy, hepatocyte, centrilobular, minimal
		lung	- histiocytosis, alveolar, minimal
		lymph node, axillary	- hyperplasia, lymphocyte/plasmacyte, medulla, mild corresponds to macroscopic observation (lymph node, axillary - enlarged)
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b)
		nerve, sciatic	- hyperplasia, lobular, minimal
		nose, level a	- within normal limits
		nose, level b	- inflammation, hair follicle/epidermis, minimal
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits

E - Euthanized *in extremis*
^r Replacement animal

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1583 ^r	E	Microscopic oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin skin, subcutis small intestine, duodenum small intestine, ileum small intestine, jejunum	- within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - abscess, mild corresponds to macroscopic observation (skin, subcutis - abscess) - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

^r Replacement animal

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1583 ^r	E	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, moderate - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mammary tumor
1584 ^r	D	Macroscopic kidneys	- irregular surface, tan, bilateral, mild

E - Euthanized *in extremis*

D - Died on Study

^r Replacement animal

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1584 ^r	D	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - hyperplasia, focal medullary, unilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
D - Died on Study ^r Replacement animal			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1584 ^r	D	Microscopic kidneys	<ul style="list-style-type: none"> - edema, papilla, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, mild - necrosis, papillary, bilateral, severe - nephropathy, chronic progressive, bilateral, mild - corresponds to macroscopic observation (kidneys - irregular surface)
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	<ul style="list-style-type: none"> - degeneration, cystic, focal, minimal - hypertrophy, hepatocyte, centrilobular, mild
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, minimal
		nerve, sciatic	- degeneration, axonal/myelin, minimal

D - Died on Study
^r Replacement animal

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1584 ^r	D	Microscopic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

D - Died on Study
^r Replacement animal

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1584 ^r	D	Microscopic spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - hyperplasia, squamous cell, mild - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - kidney inflammation/necrosis
D - Died on Study ^r Replacement animal			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1585	S	Macroscopic liver	- mass, tan, mass a, right lateral lobe, present approximately 2.5 cm in diameter. - mass, tan, mass b, median lobe, present approximately 0.7 cm in diameter. - not identified, no grade draining node for mass a and mass b.
1585	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1585	S	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrima glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - dilatation, tubular, unilateral, mild - edema, papilla, bilateral, mild - necrosis, papillary, unilateral, mild - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1585	S	Microscopic liver	- adenoma, hepatocellular, benign, multiple, primary, incidental, not cause of death corresponds to macroscopic observation (liver - mass a; liver - mass b) - degeneration, cystic, focal, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, mild - histiocytosis, alveolar, mild
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- hyperplasia, lobular, mild
		mammary gland	- degeneration, axonal/myelin, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- hyperplasia, sex-cord/stromal, unilateral, minimal
		oviducts	- within normal limits
		pancreas	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1585	S	Microscopic parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
		pituitary gland	- within normal limits
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- degeneration/necrosis, myofiber, minimal
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, minimal
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1585	S	Microscopic thymus	- depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, mild
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
1586	D	Macroscopic adrenal glands	- enlarged, red, right, minimal
		foot/feet	- absent portion/cannibalized, left foreleg/limb, no grade corresponds to antemortem observation (cannibalized/partially cannibalized)
		pituitary gland	- enlarged, red, mild

S - Scheduled necropsy
D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1586	D	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, severe corresponds to macroscopic observation (adrenal glands - enlarged) - hyperplasia, focal cortical, unilateral, minimal - pheochromocytoma, benign, unilateral, primary, incidental, not cause of death
		aorta	- within normal limits
		bone marrow, femur	- hyperplasia, granulocytic, mild
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), mild
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- not examined autolysis too severe for diagnosis
		galt	- not examined
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1586	D	Microscopic harderian glands heart joint, tibiofemoral kidneys lacrimial glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic	- within normal limits - within normal limits - within normal limits - dilatation, tubular, bilateral, mild - edema, papilla, bilateral, mild - mineralization, pelvic, unilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal - not examined - within normal limits - hyperplasia, lobular, minimal - degeneration, axonal/myelin, minimal
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1586	D	Microscopic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - not examined - within normal limits - not examined - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1586	D	Microscopic small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - erosion/ulcer, limiting ridge, minimal - depletion, lymphoid, generalized, moderate - within normal limits - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1587	S	Macroscopic adrenal glands liver lymph node, hepatic lymph node, inguinal mammary gland skin, subcutis	- enlarged, bilateral, mild - mass, red, mass b, caudate lobe, present approximately 3.5 cm in diameter. - within normal limits draining node for mass b. - within normal limits draining node for mass a, right. - swollen/thickened, tan, generalized, mild corresponds to antemortem observation (swelling) - mass, tan, mass a, right anogenital region, present corresponds to antemortem observation (nodule) approximately 1.5 cm in diameter.
1587	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1587	S	Microscopic bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - edema, papilla, bilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1587	S	Microscopic liver	<ul style="list-style-type: none"> - adenoma, hepatocellular, benign, primary, incidental, not cause of death - corresponds to macroscopic observation (liver - mass b) - focus of cellular alteration, clear, minimal - focus of cellular alteration, eosinophilic, minimal - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal
		lung	<ul style="list-style-type: none"> - within normal limits
		lymph node, hepatic	<ul style="list-style-type: none"> - within normal limits
		lymph node, inguinal	<ul style="list-style-type: none"> - within normal limits
		lymph node, mandibular	<ul style="list-style-type: none"> - within normal limits
		lymph node, mesenteric	<ul style="list-style-type: none"> - fibroadenoma, benign, primary, mortality-independent - corresponds to macroscopic observation (skin, subcutis - mass a) - mammary tumor on 18 r-1 and 26-1 are the same tumor.
		mammary gland	<ul style="list-style-type: none"> - hyperplasia, lobular, minimal
		nerve, sciatic	<ul style="list-style-type: none"> - degeneration, axonal/myelin, minimal
		nose, level a	<ul style="list-style-type: none"> - within normal limits
		nose, level b	<ul style="list-style-type: none"> - within normal limits
		nose, level c	<ul style="list-style-type: none"> - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1587	S	Microscopic nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar	- within normal limits - hyperplasia, sex-cord/stromal, unilateral, mild - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1587	S	Microscopic spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation	- within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, mild - within normal limits - adrenal glands - enlarged - mammary gland - swollen/thickened
1588	E	Macroscopic liver	- enlarged, multiple lobes, moderate

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1588	E	Macroscopic lymph node, axillary skin, subcutis	- within normal limits draining node for mass a, right. - mass, ulcerated, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 11.0 cm in diameter, tan.
1588	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - hyperplasia, focal medullary, unilateral, minimal - within normal limits - hyperplasia, granulocytic, mild - hyperplasia, granulocytic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1588	E	Microscopic eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimial glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver	<ul style="list-style-type: none"> - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - angiectasis, minimal - focus of cellular alteration, basophilic, minimal - focus of cellular alteration, eosinophilic, minimal - hypertrophy, hepatocyte, centrilobular, mild corresponds to macroscopic observation (liver - enlarged) - necrosis, focal, minimal

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1588	E	Microscopic lung lymph node, axillary lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular	- histiocytosis, alveolar, minimal - within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - atrophy, acinar, minimal - within normal limits - within normal limits - hyperplasia, focal, pars distalis, minimal - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1588	E	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - hyperplasia, epithelial, limiting ridge, minimal - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1588	E	Microscopic uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - mammary tumor
1589	E	Macroscopic adrenal glands kidneys liver ovaries pituitary gland	- enlarged, red, right, mild - cyst, clear, bilateral, moderate - focus/foci, tan, left lateral lobe, mild - cyst, clear, right, mild - enlarged, severe
1589	E	Microscopic adrenal glands aorta bone marrow, femur	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - enlarged) - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1589	E	Microscopic bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital	- within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, tubular, bilateral, moderate corresponds to macroscopic observation (kidneys - cyst) - edema, papilla, bilateral, mild - mineralization, pelvic, bilateral, mild - mineralization, tubular, bilateral, mild - nephropathy, chronic progressive, bilateral, moderate - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1589	E	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d	- within normal limits - within normal limits - within normal limits - within normal limits - angiectasis, minimal - focus of cellular alteration, basophilic, moderate corresponds to macroscopic observation (liver - focus/foci, tan) - focus of cellular alteration, eosinophilic, moderate corresponds to macroscopic observation (liver - focus/foci, tan) - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1589	E	Microscopic ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum	- cyst, unilateral, minimal corresponds to macroscopic observation (ovaries - cyst) - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1589	E	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, minimal - within normal limits - pituitary tumor
1590	E	Macroscopic adrenal glands	- enlarged, right, mild

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1590	E	Macroscopic lymph node, inguinal skin, subcutis	- not identified, right, no grade draining node for mass a. - mass, ulcerated, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 3.0 cm in diameter. red.
1590	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	- angiectasis/cystic degeneration, focal cortical, bilateral, severe corresponds to macroscopic observation (adrenal glands - enlarged) - pheochromocytoma, benign, unilateral, primary, incidental, not cause of death - within normal limits - hyperplasia, granulocytic, mild - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1590	E	Microscopic esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - dilatation, tubular, bilateral, mild - edema, papilla, bilateral, mild - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1590	E	Microscopic liver	- hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - infiltration, mononuclear cell, minimal
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits one of pair present

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1590	E	Microscopic pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus	- within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1590	E	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mammary tumor
1591	D	Macroscopic all tissues	- within normal limits
1591	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*
D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1591	D	Microscopic bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	- within normal limits - within normal limits - within normal limits - within normal limits - cataract, unilateral, mild - within normal limits - within normal limits - not examined - within normal limits - cardiomyopathy, minimal - within normal limits - dilatation, tubular, bilateral, minimal - edema, papilla, bilateral, minimal - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - necrosis, papillary, bilateral, moderate - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1591	D	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands	- within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - atrophy, acinar, mild - within normal limits one of pair present
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1591	D	Microscopic pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue	- within normal limits - hyperplasia, focal, pars distalis, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1591	D	Microscopic trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - kidney inflammation/necrosis
1592	E	Macroscopic lymph node, inguinal pituitary gland skin, subcutis stomach, glandular	- not identified, right, no grade draining node for mass b. draining node for mass a, left. - enlarged, mild - mass, tan, mass b, right inguinal area, present approximately 2.5 cm in diameter. - mass, ulcerated, mass a, left inguinal area, present corresponds to antemortem observation (mass 1) approximately 3.0 cm in diameter, tan. - swollen/thickened, mucosa, mild

E - Euthanized *in extremis*

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1592	E	Macroscopic thymus	- small, moderate
1592	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- not examined
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1592	E	Microscopic kidneys	<ul style="list-style-type: none"> - cyst, unilateral, minimal - edema, papilla, bilateral, mild - hyperplasia, transitional cell, bilateral, mild - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	<ul style="list-style-type: none"> - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - macrophages, pigmented, minimal - necrosis, individual hepatocyte, minimal
		lung	- within normal limits
		lymph node, inguinal	- within normal limits
		lymph node, mandibular	- erythrocytosis/erythrophagocytosis, sinus, minimal
		lymph node, mesenteric	- within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1592	E	Microscopic mammary gland	- adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b)
		nerve, sciatic	- hyperplasia, lobular, moderate
		nose, level a	- degeneration, axonal/myelin, minimal
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1592	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death - hyperplasia, diffuse, pars distalis, mild corresponds to macroscopic observation (pituitary gland - enlarged) adenoma is small.
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1592	E	Microscopic stomach, glandular	- fibrosis, mild corresponds to macroscopic observation (stomach, glandular - swollen/thickened)
		stomach, nonglandular	- within normal limits
		thymus	- not examined
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- dilatation, gland/lumen, minimal
		vagina	- within normal limits
		non-correlated macro observation	- thymus - small
		Cause of Death	- mammary tumor
1593	S	Macroscopic adrenal glands	- cyst, clear, right, mild - enlarged, left, mild

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1593	S	Macroscopic kidneys lymph node, inguinal skin, subcutis	- irregular surface, bilateral, mild - within normal limits draining node for mass a, left. - mass, tan, mass a, left anogenital region, present corresponds to antemortem observation (swelling) approximately 4.0 x 3.5 x 1.5 cm.
1593	S	Microscopic adrenal glands aorta bone marrow, femur	- adenoma, cortical, benign, unilateral, primary, incidental, not cause of death corresponds to macroscopic observation (adrenal glands - enlarged) - angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - cyst) - atrophy, cortical, unilateral, moderate one medulla present - within normal limits - hyperplasia, granulocytic, mild
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1593	S	Microscopic bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1593	S	Microscopic kidneys	<ul style="list-style-type: none"> - dilatation, tubular, bilateral, mild - edema, papilla, bilateral, mild - hydronephrosis, bilateral, mild - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, unilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - corresponds to macroscopic observation (kidneys - irregular surface)
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- hypertrophy, hepatocyte, centrilobular, minimal
		lung	- granuloma, minimal
		lymph node, inguinal	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1593	S	Microscopic mammary gland	- fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- not examined
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1593	S	Microscopic skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, epithelial cell, minimal - within normal limits - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits - dilatation, unilateral, mild - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1593	S	Microscopic vagina	- within normal limits
1594	S	Macroscopic all tissues	- within normal limits
1594	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1594	S	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular	- within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - angiectasis, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1594	S	Microscopic lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris	- within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1594	S	Microscopic skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, epithelial cell, mild - within normal limits - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1594	S	Microscopic uterus with cervix	- dilatation, gland/lumen, minimal - hyperplasia, squamous cell, mild - within normal limits
1595	S	Macroscopic adrenal glands lymph node, mesenteric stomach, nonglandular	- enlarged, right, moderate - within normal limits draining node for mass a. - mass, tan, mass a, present approximately 0.8 cm in diameter.
1595	S	Microscopic adrenal glands aorta bone marrow, femur	- angiectasis/cystic degeneration, focal cortical, unilateral, severe corresponds to macroscopic observation (adrenal glands - enlarged) - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1595	S	Microscopic bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cataract, unilateral, mild - within normal limits - detachment, retinal, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1595	S	Microscopic liver	- angiectasis, mild - focus of cellular alteration, basophilic, mild - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- hyperplasia, lobular, mild
		mammary gland	- degeneration, axonal/myelin, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- not examined
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1595	S	Microscopic salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue	- within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - cyst, keratin, moderate corresponds to macroscopic observation (stomach, nonglandular - mass a) - depletion, lymphoid, generalized, moderate - hyperplasia, follicular cell, unilateral, minimal - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1595	S	Microscopic trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1596	D	Macroscopic animal/whole body kidneys lacrimal glands, exorbital lung with bronchi spleen thymus	- body fat depleted, mild corresponds to antemortem observation (thin) - small, right, moderate - small, bilateral, mild - focus/foci, tan, multiple lobes, mild - small, mild - small, severe
1596	D	Microscopic adrenal glands aorta	- within normal limits - within normal limits

S - Scheduled necropsy
D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1596	D	Microscopic bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined autolysis too severe for diagnosis - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1596	D	Microscopic kidneys	<ul style="list-style-type: none"> - fibrosis, bilateral, severe corresponds to macroscopic observation (kidneys - small) appears to be secondary to calculi. - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, unilateral, mild - mineralization, tubular, bilateral, minimal
		lacrimal glands, exorbital	<ul style="list-style-type: none"> - depletion, secretory, bilateral, severe corresponds to macroscopic observation (lacrimal glands, exorbital - small)
		large intestine, cecum	<ul style="list-style-type: none"> - within normal limits
		large intestine, colon	<ul style="list-style-type: none"> - within normal limits
		large intestine, rectum	<ul style="list-style-type: none"> - within normal limits
		larynx	<ul style="list-style-type: none"> - within normal limits
		liver	<ul style="list-style-type: none"> - hypertrophy, hepatocyte, centrilobular, minimal
		lung	<ul style="list-style-type: none"> - histiocytosis, alveolar, minimal corresponds to macroscopic observation (lung with bronchi - focus/foci, tan)
		lymph node, mandibular	<ul style="list-style-type: none"> - within normal limits
		lymph node, mesenteric	<ul style="list-style-type: none"> - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1596	D	Microscopic mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1596	D	Microscopic small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate corresponds to macroscopic observation (spleen - small) - within normal limits - within normal limits - depletion, lymphoid, generalized, severe corresponds to macroscopic observation (thymus - small) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - kidneys; fibrosis; bilateral, severe
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1597	E	Macroscopic kidneys liver lymph node, inguinal pituitary gland skin, subcutis	- irregular surface, bilateral, mild - discoloration, brown, multiple lobes, moderate - within normal limits draining node for mass a, left. - enlarged, red, moderate - mass, tan, mass a, left inguinal area, present corresponds to antemortem observation (mass 1) approximately 1.6 x 1.6 x 0.5 cm. - small, mild
1597	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1597	E	Microscopic eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - dilatation, tubular, bilateral, moderate corresponds to macroscopic observation (kidneys - irregular surface) - edema, papilla, bilateral, mild - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - necrosis, papillary, unilateral, minimal - nephropathy, chronic progressive, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1597	E	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic	- within normal limits - within normal limits - within normal limits - within normal limits - degeneration, cystic, focal, minimal - hypertrophy, hepatocyte, centrilobular, mild corresponds to macroscopic observation (liver - discoloration, brown) - macrophages, pigmented, minimal - necrosis, hepatocytes, centrilobular, mild corresponds to macroscopic observation (liver - discoloration, brown) - histiocytosis, alveolar, mild - not examined misidentified tissue - within normal limits - within normal limits - adenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - degeneration, axonal/myelin, minimal

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1597	E	Microscopic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin	- within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, minimal - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - not examined - degeneration/regeneration, myofiber, minimal - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1597	E	Microscopic small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, severe corresponds to macroscopic observation (thymus - small) - hyperplasia, epithelial cell, minimal - hyperplasia, c-cell, focal, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, minimal - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1597	E	Microscopic Cause of Death	- pituitary tumor
1598	E	Macroscopic lymph node, inguinal skin, subcutis	- not identified, left, no grade draining node for mass a. - mass, tan, mass a, left inguinal area, present approximately 2.0 cm diameter.
1598	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - pheochromocytoma, benign, bilateral, primary, incidental, not cause of death - within normal limits - hyperplasia, granulocytic, mild - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1598	E	Microscopic esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - edema, papilla, unilateral, minimal - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, unilateral, mild - nephropathy, chronic progressive, bilateral, mild - pyelitis, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1598	E	Microscopic liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- focus of cellular alteration, basophilic, minimal - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal - dilatation, sinus, minimal - within normal limits - fibroadenoma, benign, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - inflammation, mild - within normal limits - within normal limits - within normal limits - cyst, bilateral, minimal - within normal limits - hyperplasia, acinar cell, focal, minimal - within normal limits one of pair present - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1598	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, mild
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1598	E	Microscopic thyroid gland	- adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death
		tongue	- hyperplasia, c-cell, focal, unilateral, minimal
		trachea	- carcinoma, squamous cell, malignant, primary, fatal, positive cause of death
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- hyperplasia, simple transitional cell, minimal
		vagina	- within normal limits
		Cause of Death	- within normal limits
1599	D	Macroscopic liver	- nose/oral tumor
		lymph node, hepatic	- mass, tan, mass a, median lobe, present approximately 4.0 x 4.0 x 2.0 cm.
		pituitary gland	- within normal limits
			draining node for mass a.
			- enlarged, red, mild

E - Euthanized *in extremis*

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1599	D	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal - vacuolation, focal, bilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- not examined autolysis too severe for diagnosis
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1599	D	Microscopic kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, hepatic lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b	- mineralization, pelvic, bilateral, mild - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - carcinoma, hepatocellular, malignant, primary, fatal, positive cause of death corresponds to macroscopic observation (liver - mass a) - hypertrophy, hepatocyte, centrilobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1599	D	Microscopic nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum	- within normal limits - within normal limits - cyst, unilateral, mild - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1599	D	Microscopic small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - liver tumor
1600	E	Macroscopic adrenal glands	- enlarged, left, mild

E - Euthanized *in extremis*

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1600	E	Macroscopic kidneys lymph node, axillary lymph node, mandibular pituitary gland skin, subcutis	<ul style="list-style-type: none"> - dilatation, pelvic, bilateral, mild - within normal limits draining nodes for mass b, left and mass c, right. - within normal limits draining node for mass a, right. - enlarged, mild - mass, firm, mass b, left axillary area, present corresponds to antemortem observation (mass 2) approximately 4.9 x 4.5 x 2.4 cm, tan. - mass, firm, mass c, right axillary area, present approximately 4.0 x 2.8 x 2.0 cm, tan. - mass, tan, mass a, cervical, right, present corresponds to antemortem observation (mass 1) approximately 8.7 x 8.6 x 2.6 cm.
1600	E	stomach, glandular Microscopic adrenal glands	<ul style="list-style-type: none"> - swollen/thickened, mild - angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - enlarged)
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1600	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1600	E	Microscopic kidneys	<ul style="list-style-type: none"> - edema, papilla, bilateral, minimal - mineralization, pelvic, bilateral, minimal - necrosis, papillary, unilateral, moderate corresponds to macroscopic observation (kidneys - dilatation, pelvic) only one has appearance of pelvic dilatation (due to papillary necrosis). - nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	<ul style="list-style-type: none"> - degeneration, cystic, focal, minimal - focus of cellular alteration, basophilic, minimal - focus of cellular alteration, eosinophilic, minimal - hyperplasia, bile duct, minimal
		lung	<ul style="list-style-type: none"> - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1600	E	Microscopic lymph node, axillary lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas	- within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass c) - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1600	E	Microscopic parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		skin, subcutis	- fibrosarcoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b) collision tumor with a fibroadenoma.
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1600	E	Microscopic spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation Cause of Death	- within normal limits - degeneration, axonal/myelin, mild - hematopoiesis, extramedullary, increased, minimal - within normal limits - hyperplasia, epithelial, limiting ridge, minimal - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - hyperplasia, c-cell, focal, unilateral, minimal - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - stomach, glandular - swollen/thickened - mammary tumor

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1601	D	Macroscopic lymph node, inguinal mammary gland pituitary gland skin skin, subcutis	- not identified, bilateral, no grade draining node for mass a, b. may be encompassed in masses. - swollen/thickened, right inguinal area, mild - enlarged, mild - hair sparse, axillary, shoulder, left, mild corresponds to antemortem observation (hair sparse) - mass, tan, mass b, right inguinal area, present approximately 2.0 x 1.5 x 1.0 cm. - mass, ulcerated, mass a, left inguinal area, present corresponds to antemortem observation (mass 1) approximately 2.0 x 2.0 x 1.0 cm, tan.
1601	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1601	D	Microscopic brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - edema, papilla, unilateral, minimal - hydronephrosis, unilateral, mild - mineralization, pelvic, unilateral, minimal - necrosis, papillary, unilateral, mild - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1601	D	Microscopic liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts	<ul style="list-style-type: none"> - focus of cellular alteration, basophilic, moderate - necrosis, hepatocytes, centrilobular, moderate - within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, multiple, primary, mortality-independent - corresponds to macroscopic observation (mammary gland - swollen/thickened; skin, subcutis - mass a; skin, subcutis - mass b) - slide 18, 26-1, and 26-2. - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1601	D	Microscopic pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen	- within normal limits - within normal limits - within normal limits - hyperplasia, diffuse, pars distalis, mild corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1601	D	Microscopic stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - depletion, lymphoid, generalized, severe - adenoma, follicular cell, benign, unilateral, primary, incidental, not cause of death - cyst, follicular, unilateral, mild - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - metaplasia, squamous, mild - within normal limits - mammary tumor
1602	E	Macroscopic adrenal glands kidneys	- enlarged, right, mild - irregular surface, bilateral, mild
E - Euthanized <i>in extremis</i> D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1602	E	Macroscopic pituitary gland	- enlarged, red, moderate
1602	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, severe corresponds to macroscopic observation (adrenal glands - enlarged)
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), mild
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1602	E	Microscopic heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland	- within normal limits - within normal limits - dilatation, tubular, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, mild - within normal limits - within normal limits - hyperplasia, lobular, mild

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1602	E	Microscopic nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular	- degeneration, axonal/myelin, minimal - exudate, nasal passage, minimal - exudate, nasal passage, minimal - inflammation, minimal - metaplasia, squamous, minimal - erosion/ulcer, moderate - exudate, nasal passage, moderate - inflammation, mild - erosion/ulcer, moderate - exudate, nasal passage, moderate - inflammation, mild - cyst, unilateral, mild - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1602	E	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - erosion/ulcer, mild - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1602	E	Microscopic uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - pituitary tumor
1603	E	Macroscopic lymph node, inguinal lymph node, mandibular pituitary gland skin, subcutis	- within normal limits draining node for mass a, right. - within normal limits draining node for mass b, right. - enlarged, red, moderate - mass, tan, mass a, right anogenital region, present corresponds to antemortem observation (mass 1) approximately 8.0 cm in diameter. - mass, tan, mass b, ventral neck, present corresponds to antemortem observation (mass 2) approximately 3.5 cm in diameter.
1603	E	Microscopic adrenal glands	- atrophy, cortical, bilateral, mild

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1603	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, tubular, bilateral, minimal - edema, papilla, unilateral, minimal - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1603	E	Microscopic lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hypertrophy, hepatocyte, centrilobular, mild - infiltration, mononuclear cell, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1603	E	Microscopic nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum	- within normal limits - within normal limits - within normal limits - cyst, unilateral, mild - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1603	E	Microscopic small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, minimal - within normal limits - mammary tumor

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1604	D	Macroscopic skin	- hair sparse, cranial, ventral thorax, moderate corresponds to antemortem observation (hair sparse)
1604	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - hyperplasia, focal medullary, bilateral, minimal - within normal limits - within normal limits - within normal limits - hyperostosis, minimal - hyperostosis, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1604	D	Microscopic joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland	- within normal limits - edema, papilla, bilateral, mild - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - necrosis, papillary, bilateral, severe - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - within normal limits - within normal limits - within normal limits - fibroadenoma, benign, primary, incidental, not cause of death slide 18. - hyperplasia, lobular, minimal
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1604	D	Microscopic nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris	- within normal limits - hyperostosis, minimal - inflammation, minimal - hyperostosis, mild - hyperostosis, mild - hyperostosis, mild - cyst, unilateral, mild - fibrosis, unilateral, moderate - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - hyperplasia, focal, pars distalis, mild - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1604	D	Microscopic skin	- alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse)
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- depletion, lymphoid, generalized, moderate
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1604	D	Microscopic Cause of Death	- kidney inflammation/necrosis
1605	E	Macroscopic clitoral glands	- enlarged, red, right, mild corresponds to antemortem observation (swelling)
		kidneys	- irregular surface, bilateral, minimal
		pituitary gland	- enlarged, red, severe
		stomach, glandular	- focus/foci, red, mucosa, mild
1605	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), mild
E - Euthanized <i>in extremis</i> D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1605	E	Microscopic esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - edema, papilla, unilateral, minimal - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1605	E	Microscopic larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas	- within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - necrosis, focal, minimal - within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (clitoral glands - enlarged) - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cyst, bilateral, mild - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1605	E	Microscopic parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, minimal

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1605	E	Microscopic stomach, glandular	- erosion/ulcer, mild corresponds to macroscopic observation (stomach, glandular - focus/foci, red)
		stomach, nonglandular	- fibrosis, mild
		thymus	- erosion/ulcer, limiting ridge, mild
		thyroid gland	- depletion, lymphoid, generalized, moderate
		tongue	- within normal limits
		trachea	- hyperplasia, squamous cell, minimal
		ureters	- inflammation, subacute/chronic, minimal
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		Cause of Death	- pituitary tumor
1606	E	Macroscopic kidneys	- irregular surface, tan, bilateral, mild

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1606	E	Macroscopic liver lymph node, inguinal pituitary gland skin, subcutis	- focus/foci, tan, median lobe, mild - not identified, right, no grade draining node for mass a. - enlarged, red, severe - mass, tan, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 4.0 x 2.5 x 1.5 cm.
1606	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1606	E	Microscopic eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital	<ul style="list-style-type: none"> - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - dilatation, tubular, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - edema, papilla, bilateral, mild - hydronephrosis, bilateral, mild - hyperplasia, transitional cell, bilateral, mild - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - pyelitis, bilateral, minimal - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1606	E	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c	- within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, mild corresponds to macroscopic observation (liver - focus/foci, tan) - hypertrophy, hepatocyte, centrilobular, minimal - infiltration, mononuclear cell, minimal - vacuolation, focal, minimal - within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1606	E	Microscopic nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1606	E	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, mild - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, simple transitional cell, minimal - inflammation, minimal - within normal limits - within normal limits - pituitary tumor
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1607	S	Macroscopic eyes liver lymph node, hepatic pancreas pituitary gland	- cloudy, right, mild corresponds to antemortem observation (eye discolored) - mass, tan, mass a, median lobe, present approximately 2.0 cm in diameter. - mass, tan, mass b, left lateral lobe, present approximately 3.0 x 1.9 x 0.9 cm. - mass, tan, mass c, right lateral lobe, present approximately 1.1 x 0.8 x 1.0 cm. - mass, tan, mass d, caudate lobe, present approximately 1.7 x 1.5 x 1.3 cm. - within normal limits draining node for mass a, mass b, mass c, and mass d. - enlarged, mild - enlarged, moderate
1607	S	Microscopic adrenal glands aorta	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - hyperplasia, focal medullary, unilateral, minimal - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1607	S	Microscopic bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cataract, unilateral, moderate corresponds to macroscopic observation (eyes - cloudy) - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, mild - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1607	S	Microscopic kidneys	<ul style="list-style-type: none"> - edema, papilla, bilateral, mild - hyperplasia, transitional cell, bilateral, minimal - inflammation, acute, unilateral, mild - mineralization, pelvic, bilateral, mild - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1607	S	Microscopic liver	<ul style="list-style-type: none"> - adenoma, hepatocellular, benign, multiple, primary, incidental, not cause of death - corresponds to macroscopic observation (liver - mass b; liver - mass c; liver - mass d) - carcinoma, hepatocellular, malignant, primary, incidental, not cause of death - corresponds to macroscopic observation (liver - mass a) - degeneration, cystic, focal, mild - focus of cellular alteration, basophilic, mild - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, panlobular, mild - histiocytosis, alveolar, minimal
		lung	- within normal limits
		lymph node, hepatic	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- hyperplasia, lobular, mild
		mammary gland	- degeneration, axonal/myelin, minimal
		nerve, sciatic	- within normal limits
		nose, level a	
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1607	S	Microscopic nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, acinar cell, focal, moderate corresponds to macroscopic observation (pancreas - enlarged) - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1607	S	Microscopic small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1608	D	Macroscopic kidneys liver lymph node, axillary pituitary gland skin, subcutis	- irregular surface, right, mild - focus/foci, white, left lateral lobe, moderate - within normal limits draining node for mass a, right. - enlarged, red, mild - mass, tan, mass a, right axillary area, present corresponds to antemortem observation (swelling) approximately 3.0 x 2.5 x 1.0 cm. - enlarged, horn, mild
1608	D	uterus with cervix Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1608	D	Microscopic eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - edema, papilla, unilateral, minimal - mineralization, pelvic, unilateral, mild - mineralization, tubular, unilateral, mild - necrosis, papillary, unilateral, moderate - nephropathy, chronic progressive, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1608	D	Microscopic liver	<ul style="list-style-type: none"> - carcinoma, hepatocellular, malignant, primary, incidental, not cause of death - corresponds to macroscopic observation (liver - focus/foci, white) - degeneration, cystic, focal, minimal - hypertrophy, hepatocyte, centrilobular, minimal - infiltration, mononuclear cell, minimal
		lung	<ul style="list-style-type: none"> - within normal limits
		lymph node, axillary	<ul style="list-style-type: none"> - within normal limits
		lymph node, mandibular	<ul style="list-style-type: none"> - within normal limits
		lymph node, mesenteric	<ul style="list-style-type: none"> - within normal limits
		mammary gland	<ul style="list-style-type: none"> - fibroadenoma, benign, primary, mortality-independent - corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal
		nerve, sciatic	<ul style="list-style-type: none"> - degeneration, axonal/myelin, minimal
		nose, level a	<ul style="list-style-type: none"> - within normal limits
		nose, level b	<ul style="list-style-type: none"> - within normal limits
		nose, level c	<ul style="list-style-type: none"> - within normal limits
		nose, level d	<ul style="list-style-type: none"> - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1608	D	Microscopic ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1608	D	Microscopic spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, mild corresponds to macroscopic observation (uterus with cervix - enlarged) - granular cell tumor, benign, primary, incidental, not cause of death - within normal limits - pituitary tumor
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1609	D	Macroscopic kidneys lymph node, inguinal pituitary gland skin, subcutis	- irregular surface, bilateral, mild - not identified, right, no grade draining node for mass a. - enlarged, red, mild - mass, tan, mass a, right anogenital region, present corresponds to antemortem observation (mass 1) approximately 4.0 x 3.0 x 3.0 cm. - swollen/thickened, limiting ridge, mild
1609	D	stomach, nonglandular Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate one medulla present - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1609	D	Microscopic esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - edema, papilla, unilateral, minimal - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, unilateral, minimal - necrosis, papillary, bilateral, severe - nephropathy, chronic progressive, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1609	D	Microscopic larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, acinar cell, focal, minimal - not examined - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1609	D	Microscopic pituitary gland	- hyperplasia, diffuse, pars distalis, mild corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1609	D	Microscopic thyroid gland	- carcinoma, follicular cell, malignant, unilateral, primary, incidental, not cause of death
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- dilatation, gland/lumen, mild
		vagina	- within normal limits
		non-correlated macro observation	- stomach, nonglandular - swollen/thickened
		Cause of Death	- kidney inflammation/necrosis
1610	E	Macroscopic pituitary gland	- enlarged, severe
1610	E	Microscopic adrenal glands	- within normal limits
		aorta	- within normal limits
		bone marrow, femur	- within normal limits

E - Euthanized *in extremis*

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1610	E	Microscopic bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	 - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1610	E	Microscopic liver	- hematopoiesis, extramedullary, minimal - hypertrophy, hepatocyte, centrilobular, minimal
		lung	- histiocytosis, alveolar, minimal
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, mild
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	one of pair present - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1610	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, minimal
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1610	E	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1611	E	Macroscopic lymph node, inguinal pituitary gland skin, subcutis	- not identified, left, no grade draining node for mass a. - enlarged, mild - mass, cystic, left inguinal area, mass a, present corresponds to antemortem observation (mass 1) mass a is approximately 6.5 cm in diameter, red, surrounded by approximately 97.0 ml. of fluid and a thin capsule.
1611	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1611	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - edema, papilla, unilateral, minimal - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1611	E	Microscopic lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - degeneration, cystic, focal, minimal - focus of cellular alteration, basophilic, mild - hypertrophy, hepatocyte, centrilobular, mild - infiltration, mononuclear cell, minimal - histiocytosis, alveolar, minimal - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1611	E	Microscopic nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical	- within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1611	E	Microscopic spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, minimal - within normal limits - mammary tumor
1612	S	Macroscopic all tissues	- within normal limits

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1612	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1612	S	Microscopic kidneys	- edema, papilla, bilateral, minimal - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- degeneration, cystic, focal, minimal - hypertrophy, hepatocyte, centrilobular, mild
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, mild
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
S - Scheduled necropsy			